NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

BRAINTREE LABORATORIES, INC.

Plaintiff

v.

NOVEL LABORATORIES, INC.,

Defendants

Case No. 3:11-cv-01341-PGS-LHG

MEMORANDUM OPINION

SHERIDAN, District Judge.

INTRODUCTION

This matter is before the Court on remand from the Federal Circuit. The Federal Circuit reversed this Court's decision granting summary judgment in favor of Plaintiff, Braintree Laboratories, Inc. ("Braintree") and findings that Defendant, Novel Laboratories, Inc. ("Novel") infringed Claims 15, 18, 19, 20, and 23 of the '149 patent. That reversal was based upon the Federal Circuit's finding that two claim terms—"clinically significant electrolyte shifts" and "patient"—were improperly construed by this Court. Specifically, the Federal Circuit defined the term "clinically significant electrolyte shifts" and the term "patient," and directed the Court to find whether "SUPREP avoids" producing any "alterations in blood chemistry [electrolyte] that are outside the normal upper or lower limits of their normal range" in the general class of persons to whom the patent compositions are directed, i.e. a patient population. *Braintree Labs., Inc. v. Novel Labs., Inc.*, 749 F.3d 1349, 1356, 1357 (Fed. Cir.), *cert. denied*, 135 S. Ct. 764 (2014). On remand, the Federal Circuit ordered this Court to review the issues of fact—that is, the electrolyte shifts

experienced by some of the patients in clinical trials—in light of their "clinical significance." This Court conducted a hearing and limited the proofs to that inquiry.

During that hearing the Court acted as the trier of fact and it adopted the standards which are ordinarily utilized by a jury to evaluate the credibility and weight of the evidence. See, Model Jury Charges of the Third Circuit, §§ 1.5, 1.6, and 1.7.

LEGAL STANDARD

Braintree has the burden of proving infringement by a preponderance of the evidence. *Siemens Med. Solutions USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1279 (Fed. Cir. 2011). To satisfy the preponderance standard, Braintree need not produce "definite" proof of infringement, but must instead demonstrate that "infringement was more likely than not to have occurred." *Warner-Lambert Co. v. Teva Pharaceuticals, USA, Inc.*, 418 F.3d 1326 (2005)

Courts use a two-step analysis to determine infringement under 35 U.S.C. § 271. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). "[F]irst, the court determines the meaning of the disputed claim terms, then the accused device is compared to the claims as construed to determine infringement." *Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 804 (Fed. Cir. 2007). Literal infringement is proven when each and every claimed limitation is present in the accused product. *Renishaw PLC v. Marposs Societa' per Azioni,* 158 F.3d 1243, 1247-48 (Fed. Cir. 1998). Application of a patent claim to an accused product is a fact-specific inquiry. *Kustom Signals, Inc. v. Applied Concepts. Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001).

In addition, 35 U.S.C. § 271(e)(2)(A) provides that it shall be an act of infringement to submit an Abbreviated New Drug Application ("ANDA") "if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent." The

infringement analysis compares the asserted claims and the proposed generic product that is likely to be sold following FDA approval. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997); *see also Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002).

FINDINGS OF FACT

In light of the testimony, including the credibility of witnesses and the evidence of proof, the Court finds the following facts:

1. The parties agreed that the following claims, 15, 18, 19, 20, and 23 of the '149 patent are in issue. Claims 15 and 18 are independent composition claims. Claims 19, 20, and 23 are dependent method claims.

Patient Population

2. As noted above, the federal circuit defined patient population to be "the general class of persons to whom the patent composition are directed." *Braintree*, 749 F.3d at 1356, 1357.

3. In order to determine whether the "percentage" or the "means" approach was appropriate, there was a need to determine what constitutes "patient population."

4. In order to evaluate the general class of patient or the patient population, the parties agreed that patient population includes a person that a doctor has said has a need for a colonoscopy. There are two categories of such people: 1) people over 50 who have colonoscopies for screening for polyps and cancer; and 2) people of any age who have some need for intestinal surgery or other procedure requiring a clear colon.

5. The general class of persons to whom SUPREP is directed is more limited than the broader rules above: adults who are indicated for colonoscopy and who do not have a contraindication for SUPREP. Tr. 153:24- 154:21, 156:5-14, 157:7-13 (Peura Direct); Tr. 32:24-33:3, 63:22-25 (Heitjan Direct); see also 249:1-23 (Sconzo Direct).

6. A person is "indicated for" colonoscopy if a healthcare provider has made a decision that there is a reason for the patient to undergo colonoscopy. A "contraindication" is a condition for which a certain medication should not be administered because the medication may have an adverse effect on the patient's health. Tr. 153:24-154:21, 157:7-13 (Peura Direct).

7. The contraindications for SUPREP are listed in the SUPREP label. Patients suffering from these conditions would not be included in the SUPREP patient population. Tr. 154:22-156:14 (Peura Direct); PTX076 (SUPREP Label) at BRTSUP00000129.

Clinical Trials

8. It was uncontroverted that there were four SUPREP clinical trials conducted by Braintree at the direction of the FDA. Each study constituted of patients within the patient population. Braintree's and Novel's experts (Dr. Heitjan and Dr. Goldfarb, respectively) used those trials to support their findings.

9. There are four SUPREP clinical trials: BLI800–301; BLI800–302; BLI800–303; and BLI800– 202 (collectively "the SUPREP clinical trials"). Tr. 55:23–56; PDX11–8, 11-10 (Heitjan Slides).

10. BLI800 – 301 involved 194 subjects randomly assigned to receive SUPREP and 193 subjects randomly assigned to receive a prep called MoviPrep. All subjects received two bottles of the prep, 1-3 hours apart, on the day before colonoscopy. Three blood draws were taken: one screening draw several days before taking the prep, one just before colonoscopy after the second bottle was taken, and one about a month after the colonoscopy. Tr. 57:9-58:6 (Heitjan Direct); PDX11-7 (Heitjan Slides); PTX411 (BLI800-301 Clinical Study Report).

11. BLI800-302 involved 181 subjects randomly assigned to receive SUPREP and

183 subjects randomly assigned to receive MoviPrep. Taking a split-dose regimen for SUPREP, the subjects receiving SUPREP took two bottles of the prep 10 to 12 hours apart. Three blood draws were taken, with the same timing as in the 301 study. Tr. 58:7- 19 (Heitjan Direct); PDX11-8 (Heitjan Slides); PTX387 (BLI800-302 Clinical Study Report); PTX76 (SUPREP Label) at 2.

12. BLI800-303 involved 63 subjects randomly assigned to receive SUPREP and 67 subjects randomly assigned to receive NuLytely. Consistent with the FDA-approved split-dose regimen for SUPREP, the subjects receiving SUPREP took two bottles of the prep 12 hours apart. Two blood draws were taken: one at screening (before the prep was taken), and one just before colonoscopy after the second bottle was taken. Tr. 58:20-59:9 (Heitjan Direct); PDX11-9 (Heitjan Slides); PTX394 (Rex 2010 Article); PTX76 (SUPREP Label) at 2.

13. BLI800-202 was a pharmacokinetic/pharmacodynamic study, in which frequent blood measurements are taken to determine the time course of any effects of treatment. The study involved 18 subjects: 6 healthy, 6 with moderate renal impairment, and 6 with mild/moderate hepatic impairment. All subjects received two bottles of SUPREP 12 hours apart. The subjects had three pre-treatment ("baseline") blood draws – one at a screening visit, one a day before taking the prep, and one immediately before the first bottle. They also had many blood draws after taking the prep: at 1, 2, 4, 8, and 10 hours after the first bottle, 10 minutes before the second bottle, 1, 2, 4, 8, 12, and 18 hours after the second bottle, and before noon on follow up days 3 and 6. No colonoscopies were performed. Tr. 59:10-60:14 (Heitjan Direct); PDX11-10 (Heitjan Slides); PTX410 (BLI800-202 Clinical Study Report).

14. BLI800-301 and 302 had the same normal ranges for each electrolyte measured. The 202 and 303 studies had different normal ranges than the 301 and 302 studies. Because of these differences, an electrolyte value could be inside the normal range for one study but outside

the normal range for another study. Tr. 61:1-9; 63:10-21 (Heitjan Direct); PDX11-11 (Heitjan Slides); PTX410 (BLI800-202 Clinical Study Report) at 219, 224; PTX411 (BLI800-301 Clinical Study Report) at 47; PTX387 (BLI800-302 Clinical Study Report) at 45; PTX394 (Rex 2010) at 335.

Witnesses

15. Each party presented two witnesses. Braintree's witnesses were Dr. Heitjan and Dr. Peura. Novel's witnesses were Dr. Goldfarb and Dr. Sconzo. A brief description of each witness's experience is set forth below.

16. Dr. Daniel Heitjan is currently a professor of statistical science at Southern Methodist University, and professor of biostatistics at the University of Texas Southwestern Medical Center. Tr. 29:7-6 (Heitjan Direct). He was previously a statistics professor at the University of Pennsylvania for 11 years. PTX486 (Heitjan CV). Dr. Heitjan has many years of experience in the design, conduct, and analysis of clinical trials, and in particular in the interpretation of clinical trial data. T32:8-11 (Heitjan Direct); Tr. 133:20-124:10 (Heitjan Re-Direct); PTX486 (Heitjan CV). The Court admitted Dr. Heitjan as an expert in biostatistics. Tr. 30:14-31:5 (Heitjan Direct). Dr. Heitjan is not a person of ordinary skill in the art ("POSITA") as defined during the original trial.

17. Dr. David Peura, a gastroenterologist, has served as an emeritus professor at the University of Virginia since 2008. ECF No. 380 ("Validity Op.") at 4; PTX485 (Peura CV). Dr. Peura is an expert in gastroenterology, gastrointestinal procedures, and the use of preparations to prepare patients for gastrointestinal procedures. Validity Op. at 5. Dr. Peura is also an expert with respect to electrolyte shifts and transfers that take place when an osmotic laxative, like SUPREP, is ingested. Tr. 146:14-25 (Peura Direct).

18. Dr. David Goldfarb testified at the original trial. He is a nephrologist who specializes in diagnosing, assessing, and treating kidney diseases, including diseases associated with electrolytes, fluid, and electrolyte balance. Tr. 288:5-9, 289:12-17; Tr. 113:17-23, 260:14-22, 261:12-20. Dr. Goldfarb is an expert in electrolytes, electrolyte shifts, and evaluating electrolyte physiology in response to the administration of a bowel prep. Tr. 289:18-25. Dr. Goldfarb is a POSITA as it relates to the '149 patent. Tr. 300:16-24.

19. Dr. Sconzo is a gastroenterologist who regularly practices in Long Island. He is board certified for colon-rectal surgery by the Fellow American College of Surgeons and the Fellow American College of Colon Rectal Surgeons. DTX691 (Sconzo CV). Dr. Sconzo is a POSITA as defined in the original trial. Tr. 248:4-6. He was admitted as an expert in "colorectal surgery, including administration of colonoscopies, and the use of preps to prepare patients for colorectal surgical procedures." Tr. 246:11-19.

Credibility of Witnesses

20. Braintree's witnesses were more credible than Novel's witnesses. More specifically, Dr. Goldfarb testified honestly and comprehensively at the original trial; but here his testimony was riddled with minor errors, and this Court finds it was less than credible. Therefore, Dr. Goldfarb's testimony is given less weight than that of Dr. Heitjan and Dr. Peura. Dr. Goldfarb admitted to some mistakes which are detailed in paragraphs 21-25 below.

21. Dr. Goldfarb admitted that at least two of the patients he identified as having clinically significant electrolyte shifts caused by SUPREP in the 303 study never took SUPREP. Tr. 387:16-22 (Goldfarb Cross).

22. Dr. Goldfarb testified that Patient 4001 in the 303 study had a potassium shift caused by SUPREP. Tr. 383:23-384:2 (Goldfarb Cross). During the 303 study, Patient 4001 took

NuLytely, a large volume, isotonic colon prep, but did not take SUPREP. Tr. 385:6-7 (Goldfarb Cross); PTX454B at BRTSUP000124959. Dr. Goldfarb admitted that SUPREP did not cause the electrolyte shift in Patient 4001. Tr. 385:8-10 (Goldfarb Cross).

23. Dr. Goldfarb testified that Patient 4029 in the 303 study had a bicarbonate shift caused by SUPREP. Tr. 386:17-19 (Goldfarb Cross). Patient 4029 took NuLytely, but did not take SUPREP. Tr. 387:8-12 (Goldfarb Cross); PTX454B at BRTSUPOO 124959. Dr. Goldfarb incorrectly concluded Patient 4029 had a bicarbonate shift caused by SUPREP. Tr. 387:13-14 (Goldfarb Cross).

24. In addition to paragraph 18, the sample drawn from patient 4001 was grossly hemolyzed. Tr. 385:17-386:6 (Goldfarb Cross); PTX454B at BRTSUP00124972. Dr. Goldfarb admitted that the measurements for Patient 4001 were questionable because the sample was hemolyzed. Tr. 386:13-15 (Goldfarb Cross).

25. In addition, Dr. Goldfarb made other errors in the 202 and 301 studies. See, cross-examination of Dr. Goldfarb, Tr. 390:1-415:20.

26. Novel argues that Goldfarb's mistakes were unintentional and did not undermine his substantive findings. Novel argues:

> On direct, Dr. Goldfarb testified that 18 out of 18 (100%) patients exhibited outside-of-normal range shifts in the 202 Study, 80 out of 180 (44%) patients exhibited outside-of-normal range shifts in the 302 Study, and 20 out of 63 (32%) patients exhibited outside-of-normal range shifts in the 303 Study. Tr. at 325:4-17, 330:9-18, 352: 17-353: 1. Dr. Goldfarb was the only expert to have actually reviewed the thousands of pages of clinical trial data in this case. Tr. at 382:17-19. In doing so, Dr. Goldfarb made three mistakes in summarizing the data associated with two patients from the 303 Study and one patient from the 301 Study. Dr. Goldfarb never intended to mislead the Court (Tr. at 435:9-15), and while unfortunate, his mistakes should not cast doubt on the fact that SUPREP administration caused abnormal shifts. Indeed, Dr. Goldfarb's testimony,

> aside from the three inadvertent mistakes, was unrebutted by either of Braintree's experts.

Novel Br. at 30 n.9.

27. The Court rejects Novel's argument (paragraph 26) concerning Goldfarb's testimony because the inconsistencies demonstrated a lack of a thorough analysis of the data presented in the clinical trials. As such, the Court gave little weight to Goldfarb's testimony compared to Heitjan and Peura.

28. Dr. Sconzo testified in a credible manner. His testimony concerned a practitioner's viewpoint. That is, Dr. Sconzo "never discusses issues concerning bowel prep choice with his patients in the context of mean data." Tr. 262:25-263:1, 263:3-8. Instead, Dr. Sconzo testified that he "looks at individual patients within the general patient population." Novel Br. at 9. Despite the testimony, the Court cannot rely on a practitioner who cannot give substantive testimony on the electrolyte shifts within a patient. The Court gives little weight to Dr. Sconzo's testimony.

29. Dr. Peura's testimony was credible except for on one point. That is, Dr. Peura testified that he did not know of any untoward effects from the use of SUPREP; however, Dr. Peura admitted that he did not research the Med Watch section of the FDA website, nor did he inquire of Braintree whether there were any adverse effect reports.

30. When Dr. Peura testified, I did not admit DTX715, but the parties agreed to a more limited proffer. The parties entered a stipulation into evidence as exhibit DTX715. The stipulation reads:

> Plaintiff Braintree Laboratories, Inc. and Defendant Novel Laboratories, Inc. have met and conferred regarding DTX707, DTX708, DTX709, DTX710, and DTX715. The parties hereby stipulate, subject to the Court's approval, to the following:

> Defendant Novel Laboratories, Inc. and Plaintiff Braintree Laboratories, Inc. hereby stipulate to the admissibility of DTX715 for the limited purpose of showing that the reports contained in DTX7 I 5 were filed with the United States Food and Drug Administration, are kept on file with FDA, and are available to the public through FOIA request. DTX715 (bearing the Bates range NOV00l1047-77) contains the pages corresponding to the following exhibits, marked separately for identification at trial as: DTX707 (NOV0011066-67), DTX708 (NOV00l1074-77), DTX709(NOV0011053-55), and DTX710(NOVOl1067-68). Novel withdraws its offer of DTX707, DTX708, DTX709, and DTX710.

31. Based on Dr. Peura's unfamiliarity with the Med Watch report and his failure to ask Braintree about untoward effects, his testimony regarding same is suspect. This broad statement of not being aware of any untoward effects of SUPREP on patients is incredulous since he did not perform any research. Except for this point, the Court found Dr. Peura to be a credible witness. However, the untoward effects argument raised by Novel in its cross-examination of Dr. Peura had no effect on the outcome of this hearing because it was not evidence of clinically significant electrolyte changes in the patient population. Anecdotal evidence is of little relevance.

Mean v. Percentage

32. Dr. Heitjan, a biostatistician, insists that the best approach to answer the Federal Circuit's query regarding whether the patient population had alteration of electrolytes outside the normal range is to utilize a means analysis.

33. According to Dr. Heitjan, a means analysis is a standard or fundamental approach to address patient population inquiries, and it is the most basic concept he teaches to his students. (Tr. 45:12-17). Dr. Heitjan stated:

> Well, in statistics we have lots of tools for conducting different kinds of analyses, for answering different kinds of questions. So we're always looking for the right tool that will answer the question that's

> being specified. And that's relevant here because the Circuit Court has been very specific about saying what kind of analysis needs to be done, that is looking for clinically significant shifts referring to shifts outside of the normal range in a particular population. So those directives lead me as a statistician specifically to analyze means looking at changes in the means.

34. Novel's approach is different from Dr. Heitjan's methodology. Novel argues that the Federal Circuit requires a percentage approach to determine if there are clinically significant electrolyte shifts. That is, to determine the percentage of the patient population that are not within the normal range of electrolyte levels. This is accomplished by inserting numerical factors into the following formula:

$$\frac{\text{The number of patients outside of normal range}}{\text{Patient Population}}$$

Novel's argument relies on the text of Federal Circuit opinion. Novel argues:

> There is not a single instance in the Federal Circuit decision where the Court mandates that use of "mean" or "average" data to measure clinically significant electrolyte shifts in a patient population. Tr. 54:22-25. In fact, the opposite is true. All three members of the appellate panel addressed the issue of clinically significant electrolyte shifts in the context of percentage of patients, not a mean analysis. In the majority opinion, Judge Prost referenced "a large percentage of patients" -- not an "average" of the entire patient population as Braintree's experts now posit-when describing the absurdity of Braintree's initial proposed construct on for a patient as meaning "one or more." *Braintree Labs.*, 749 F.3d at 1357. Likewise, Judge Dyk, in his concurrence/dissent, referenced "the percentage of individuals experiencing such electrolyte shifts," "a majority of patients," and "a significant minority or about one-third of patients" when discussing measurement of electrolyte shifts. *Braintree Labs.*, 749 F.3d at 1361 n.1. Finally, in dissent, event Judge Moore characterizes clinically significant electrolyte shifts as occurring in a "percentage of people," a "statistically significant number of people" or a "majority" not in a mean or average of the entire patient population taking SUPREP as Braintree's experts would have this Court believe. *Id.* at 1367, n.3

Dr. Goldfarb's opinion was of concern. He noted that a major fraction of hundreds of

patients demonstrated the existence of clinically significant electrolyte shifts; however on cross-examination he stated that a major fraction is a "qualitative" number. (Tr. 431:21-433:24). The use of the word "qualitative" gave rise to the question about whether the percentage analysis was valid because it may vary among POSITAs. As such, the opinion of Dr. Goldfarb was given less weight.

35. In addition, Novel relied upon Dr. Goldfarb's testimony and who Novel argues that his testimony is in accordance with FDA analysis. Dr. Goldfarb opined that percentage analysis was more appropriate. Novel noted:

> Importantly, FDA findings corroborate Dr. Goldfarb's opinion that SUPREP produces clinically significant electrolyte shifts in a significant portion of the general class of persons to whom the '149 patented invention is directed. FDA reviewers were "particularly attentive to the impact of SUPREP on fluid and electrolyte disturbances." DTX675 at FDACDER00026. That means that "since everyone understands that hypertonic bowel preps are associated with changes in the balance of electrolytes and lead to these kinds of clinically significant effects, the inventors, the investigators, and the FDA were all going to pay attention to the effect of SUPREP on fluids and electrolytes." Tr. 340:14-23. "The specific abnormalities of interest included low serum bicarbonate, high BUN, high creatinine, high uric acid, high magnesium, and high/low chloride, sodium, potassium, phosphate and osmolality." DTX675 at FDACDER00027. The FDA's approach of evaluating SUPREP's effect on electrolytes and blood chemistry is that the '149 patent inventors and Dr. Goldfarb took, and inconsistent with the approach of Dr. Heitjan's and Peura. [Tr. 341:6-13.]

36. Despite Novel's argument that the Federal Circuit mandated the percentage approach, Dr. Heitjan states that the issue presented concerns a patient population and requires a mean analysis. He noted:

> Right. So the Circuit Court is saying you need to look not at a patient, but at the patient population. The second element of what they're saying is you need to look for clinically significant differences which would be effects of moving, you know, shifts outside of the normal range. So I interpret that as saying well, we

> need to look at the mean because that's the parameter that's relevant to the population. So we see if the means shift outside of the normal range. Tr. 55:14-22.

37. The testimony of Dr. Heitjan and Dr. Peura demonstrated that the percentage omits factors which the mean analysis considers. For instance, the percentage approach does not measure variability of the patient population, but the means approach does so.

38. Dr. Heitjan explained variability. When an individual characteristic, such as electrolyte level is measured, there is variability. Heitjan, as a biostatistician, describes this as "between-subject" and "within-subject" variability. "Between subject" variability refers to differences in measurements between different people. "Within subject" variability refers to differences in measurements taken from one individual over time. Tr. 42:6-44:2 (Heitjan Direct).

39. Dr. Peura agreed with Dr. Heitjan's variability argument for several similar reasons. Dr. Peura testified that variability may affect electrolyte levels in terms of intrinsic, extrinsic and analytic variables. Tr. 171:20-172:14 (Peura Direct).

40. Intrinsic factors that can affect electrolyte levels include age, gender, exercise, ethnicity, and whether the patient is using other drugs. Tr. 172:15-173:6; 178:13-180:9 (Peura Direct); PTX396; PDX12-9 (Peura Slides). Extrinsic factors that can affect electrolyte levels include fasting, dehydration, time of blood draw, stress, and hyperventilation. These factors are present in the context of colonoscopy preps. Tr. 173:7-174:7 (Peura Direct); PDX12-10 (Peura Slides).

41. Dr. Peura testified that extrinsic and intrinsic factors may result in a biologic variation. For example, if blood is drawn from a person once a week for ten weeks and an analyte is measured in each blood draw, it is unlikely that all ten values would be the same. As a result, the mean approach considers such variability accruing due to the number of blood draws.

Tr. 182:11-16 (Peura Direct); PTX397 ("Clinical Chemistry") at 6-7.

42. As noted in paragraph 39 above, analytic factors may also affect electrolyte levels. Such analytic factors include human error, equipment variability, exposure to ambient air, hemolysis, and the length of time that a blood sample sits before analysis. Dr. Heitjan refers to this concept as "measurement error," which can cause "within subject" variability. Tr. 174:8-175:11, 177:14-178:12; 181:23-182:10 (Peura Direct); 43:1-15 (Heitjan Direct); PTX395 ("Variation, Errors, and Quality in the Clinical Laboratory") at 3, 7; PTX397 ("Clinical Chemistry") at 6-7; PDX12-11 (Peura Slides).

43. Based upon the credibility of Dr. Heitjan and Dr. Peura and the questionable credibility of Novel's experts, the Court finds the means approach is the best methodology to utilize. The primary reason for that finding are patient variability factors explained above.

44. Dr. Heitjan testified about how he applied the means approach to clinical trials:

(a) Dr. Heitjan calculated the percent of the subjects in each of the SUPREP clinical trials that had a pretreatment (or "baseline") value outside the normal range for any electrolyte. His results are presented in PTX482. In the BLI800-202 study, 44% of patients had at least one baseline serum electrolyte value outside the normal range. Baseline out-of-range results were about 30% in the BLI800-301 and 302 studies, and about 26% in the BLI800-303 study. These results show that it is common for a subject to have an electrolyte value outside the normal range without taking any colon prep, simply as a result of within-subject variability. PTX482 (All Studies Baseline Percentages); Tr. 64:17-66:13 (Heitjan Direct); PDX11-12 (Heitjan Slides).

(b) Another way to evaluate the variability in subjects' electrolyte values before they take a colon prep is by analyzing the baseline data from the BLI800-202 study, which involved three separate blood draws before the patients took any colon prep. The data is summarized in

PTX481. It shows that patients' electrolyte values moved - including with respect to the normal range - during the three baseline measurements, even though the patients had not yet been administered SUPREP. This occurred in healthy patients as well as impaired patients. This data confirms that electrolyte values can move from inside to outside the range due to within-subject variability, unrelated to a prep. PTX481 (BLI800-202: Pre-Dose Electrolyte Levels); Tr. 67:3-71:19; PDX11-13 (Heitjan slides) (animation); PDX11-14 (Heitjan slides) (animation).

(c) PTX481 shows how biologic and analytic variation can confound the interpretation of single patient blood values. Tr. 183:15-184:9 (Peura Direct); PTX481 (BLI800-202: Pre-Dose Electrolyte Levels). Because the pre-dose blood levels vary within and between subjects, the individual data gleaned from the study may not give the full explanation of what is occurring in the patient population.

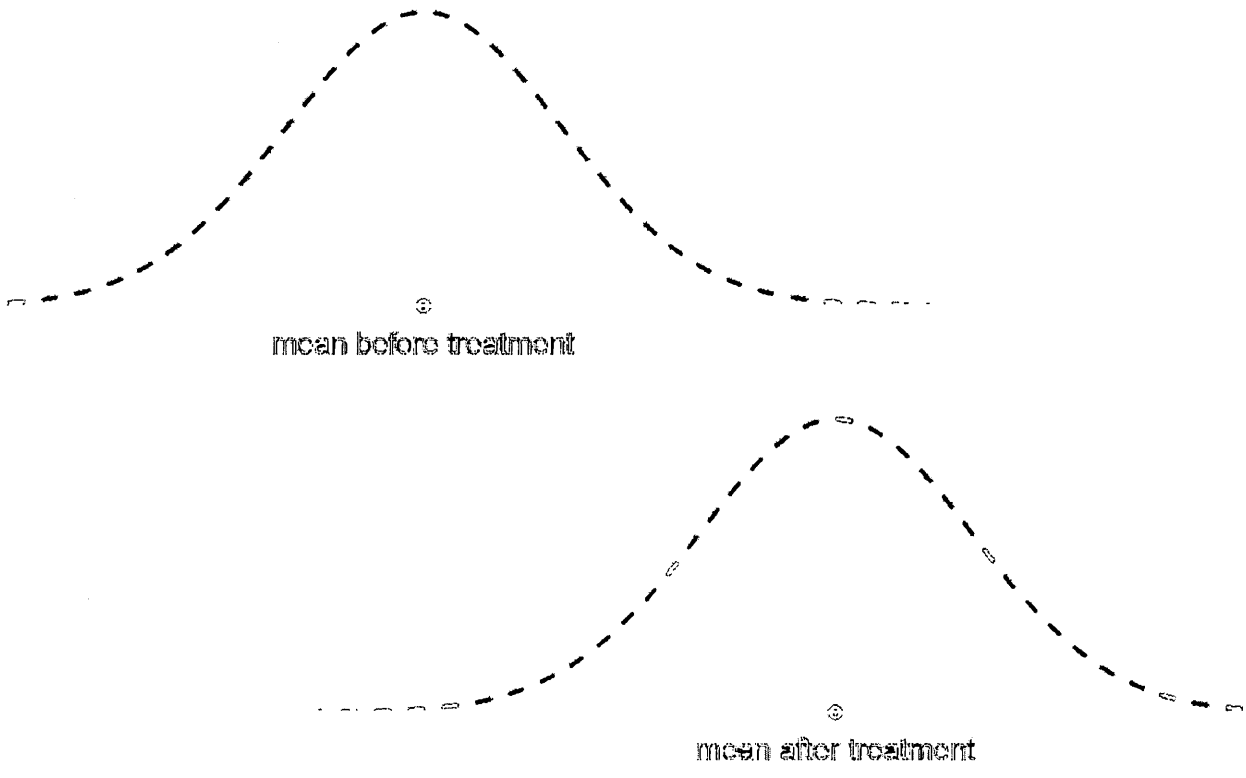
Means Approach

45. According to Dr. Heitjan, the term "mean" refers to two related concepts. The first concept is the sample mean (average). That is, if you have ten subjects and you have a value for each subject, you can calculate the sample mean by adding the values for each subject and dividing by ten. The second concept is the population mean, which refers to the mean for the entire population. The sample mean is then used to estimate the population mean. Tr. 36:18-37:13 (Heitjan Direct) (emphasis added).

46. According to Dr. Heitjan, clinical trials are conducted by drawing a representative sample from a population. You can measure a particular characteristic in the sample, such as an electrolyte level, and calculate the sample mean. The sample mean can be used to estimate the population mean. The larger the sample, the better the estimate of the population mean. Tr. 38:17-39:13 (Heitjan Direct); PDX11-4 (Heitjan Slides) (animation).

47. A "representative sample" refers to a sample in which no subset of the population – such as older people or men – are overrepresented. Tr. 39:14-20 (Heitjan Direct).

48. Typically, the individual values for a particular variable, such as an electrolyte level, are concentrated in the middle of the distribution of values, with fewer observations toward the tails of the distribution, thereby creating a bell curve shape. The individual values aggregate around the mean. An effect on the population caused by a treatment is observed by a shift in the curve and the mean. The larger the shift in the mean, the greater the effect of the treatment. Tr. 37:19-38:13 (Heitjan Direct); PDX11-3 (Heitjan Slides).



49. A confidence interval measures how precisely the sample mean estimates the population mean. It can be thought of as a range of likely values of the true population mean.

50. A 95 percent confidence interval indicates that there is a 95 percent certainty that the true population mean is within the interval. Tr. 39:21-41:3 (Heitjan Direct); PDX11-5

(Heitjan Slides). Dr. Heitjan removed several individual subjects from the top and bottom of the sample to reach the confidence interval.

51. The confidence interval is normally depicted with bars extending out from the mean, where the "width" of the confidence interval refers to the distance from the bottom to the top of the line. The confidence interval widens as the variability of the data increases, and narrows as the sample size increases. Tr. 41:4-42:4 (Heitjan Direct); PDX11-5 (Heitjan Slides).

52. The electrolytes that are measured in the blood are bicarbonate, calcium, chloride, magnesium, phosphorus, potassium, and sodium. Tr. 159:7-20 (Peura Direct); PTX490, at 439, Appendix C (FDA Manual); see also Tr. 410:3-6, 409:14-16 (Goldfarb Cross).

53. The analytes listed in the "Enzymes" and "Other" categories of the Investigations Operations Manual are not electrolytes. Tr. 159:7-23 (Peura Direct); PTX490, at 439, Appendix C (FDA Manual); Tr. 410:11-411:20 (Goldfarb Cross).

54. Dr. Heitjan conducted a means analysis of the electrolyte data from the SUPREP clinical trials. These materials included data files provided to Braintree directly by the laboratories that conducted the testing. Dr. Heitjan received data files in various formats, including SAS (the format used by the FDA) and Excel. The data files that Dr. Heitjan received were provided to the Court as PTX432. Dr. Heitjan also received data handling guidelines (PTX430) describing how Braintree handled routine data issues that arose during clinical trials. Dr. Heitjan testified that any biostatistician could have conducted the same analysis that he conducted using the data on PTX432. Tr. 88:18- 89:15 (Heitjan Direct); 114:4-13 (Heitjan Cross); 134:11-135:14, 139:9-21 (Heitjan Re-Direct); PTX432 (data disk); PTX430 (data handling guidelines)

55. Dr. Heitjan analyzed clinical trial data in the patients who took SUPREP for the seven electrolytes measured in blood serum in the SUPREP clinical trials: bicarbonate, calcium, chloride, magnesium, phosphate, potassium, and sodium. Tr. 57:1-6 (Heitjan Direct).

56. Dr. Heitjan found that, after administration of SUPREP, none of the mean serum electrolyte levels in any of the SUPREP clinical trials fell outside the upper or lower limits of the normal range for any of the seven electrolytes. The means changed little from before to after administration of SUPREP in each of the trials. Tr. 34:6-17 (Heitjan Direct); PTX483 (Heitjan SUPREP Analysis); PDX11-15 through 11-50 (Heitjan Slides).

57. For BLI800-301, Dr. Heitjan calculated the means and 95% confidence intervals for the sample population who took SUPREP for bicarbonate, calcium, chloride, magnesium, phosphate, potassium, and sodium levels. He made these calculations at baseline, at the colonoscopy time point a few hours after administration of SUPREP, and at the follow-up time point 30 days later. The means barely changed at all between these three time points for each electrolyte, and did not approach the outer limits of the normal range. Tr. 72:8-75:23 (Heitjan Direct); PTX483 (Heitjan SUPREP Analysis) at 8-14; PDX11-15 through 11-21 (Heitjan Slides).

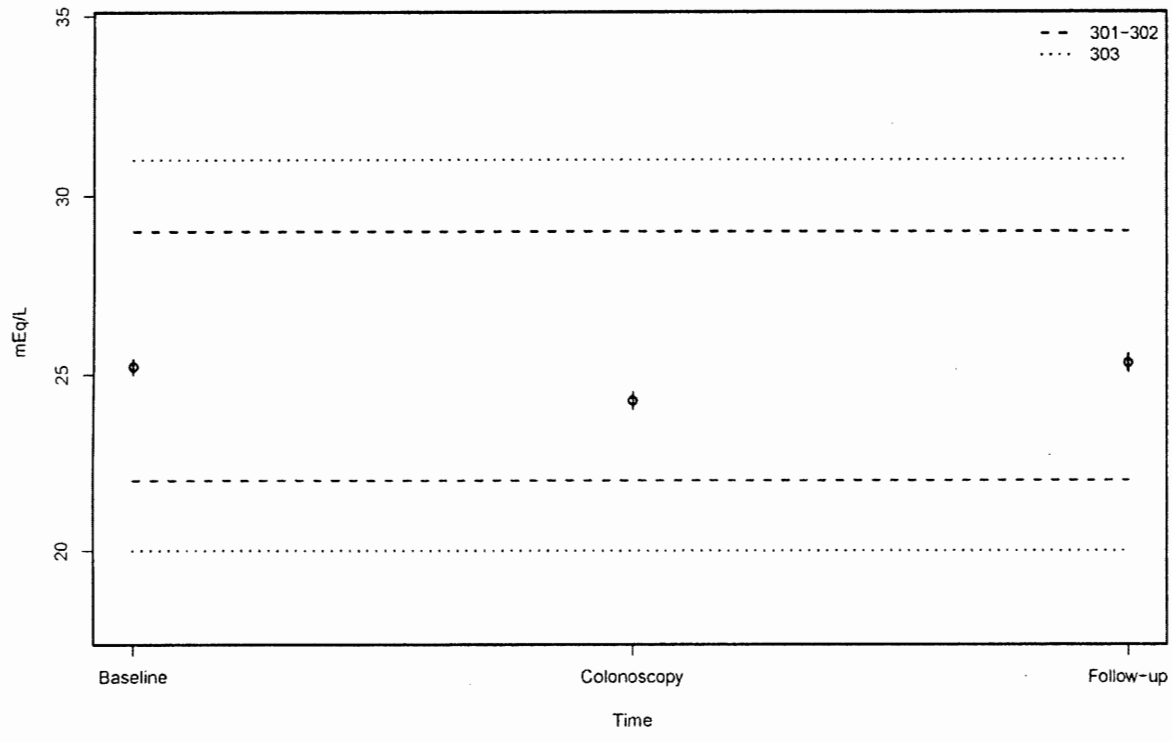
58. For BLI800-302, Dr. Heitjan conducted the same analysis as for BLI800-301. As in the 301 results, the means barely changed at all between the three time-points for each electrolyte, and did not approach the outer limits of the normal range. Tr. 75:24-77:14 (Heitjan Direct); PTX483 (Heitjan SUPREP Analysis) at 15-21; PDX11-22 through 11-28 (Heitjan Slides); see also Tr. 348:18-25, 351:1-5 (Goldfarb Direct).

59. For BLI800-303, Dr. Heitjan analyzed the two time points that were collected in the study (baseline and colonoscopy). As in the 301 and 302 results, the means barely changed at

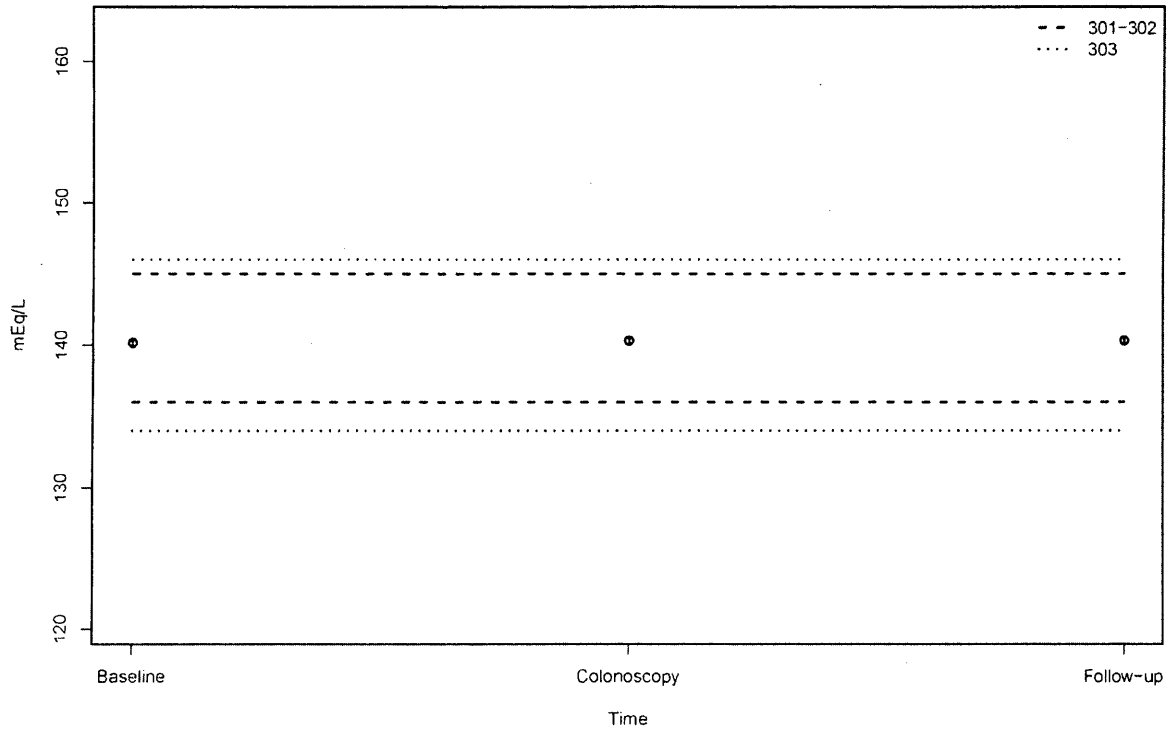
all between the time points for each electrolyte, and did not approach the outer limits of the normal range. Tr. 77:15-79:11 (Heitjan Direct); PTX483 (Heitjan SUPREP Analysis) at 22-28; PDX11-29 through 11-35 (Heitjan Slides).

60. Dr. Heitjan combined the data from the BLI800-301, 302, and 303 studies because these studies had similar eligibility requirements, and the larger sample size more precisely estimates the population mean. Dr. Heitjan calculated means and 95% confidence intervals for that combined data. The means barely changed between the time points for each electrolyte, and did not approach the outer limits of the normal range. Tr. 79:12-82:9 (Heitjan Direct); PTX483 (Heitjan Analysis) at 29-35; PDX11-36 through 11-42 (Heitjan Slides).

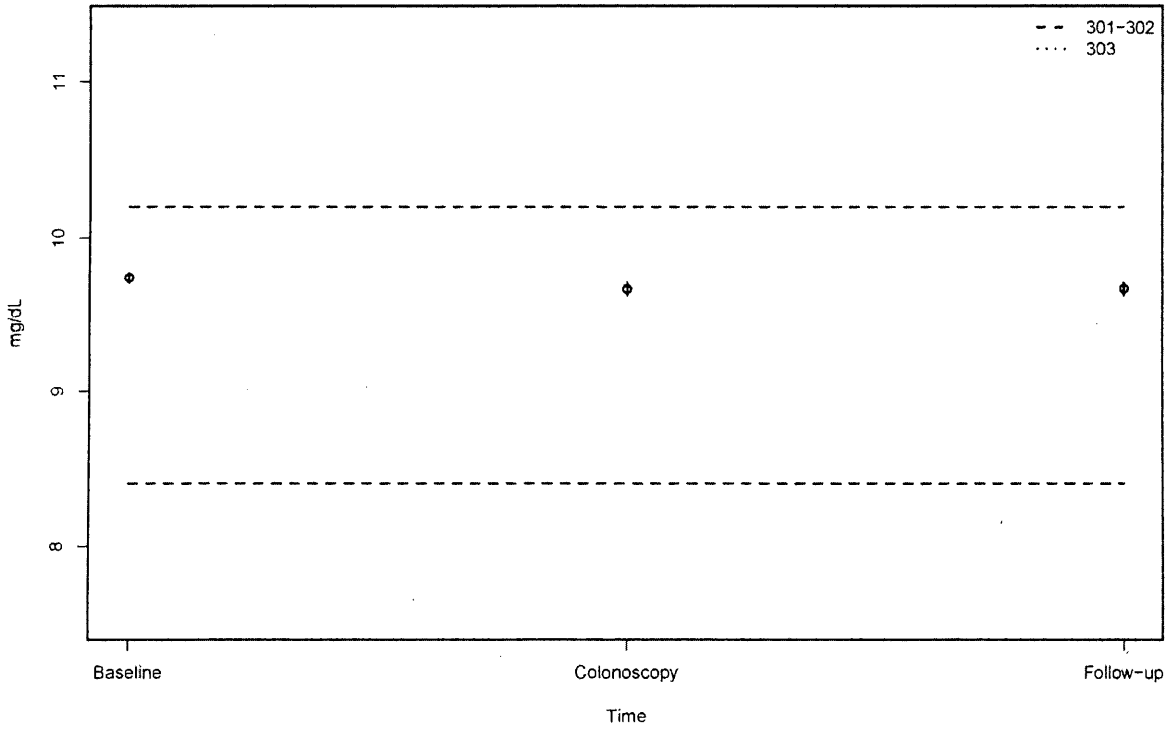
Bicarbonate:



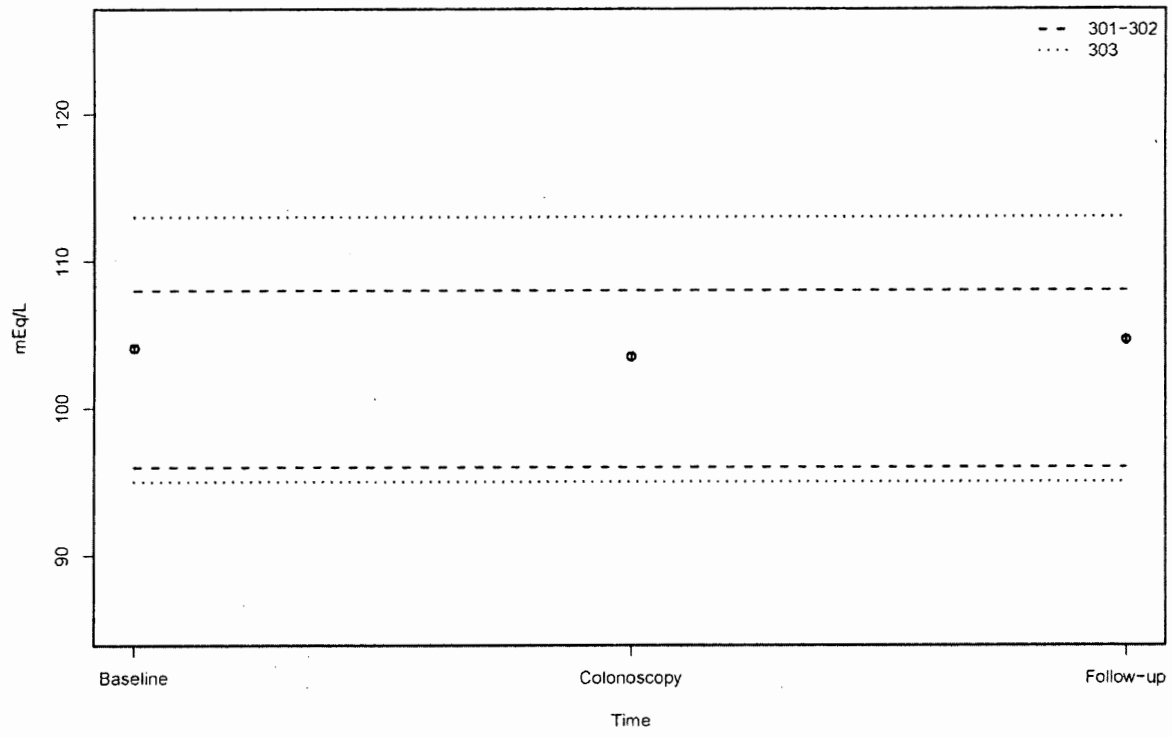
Sodium:



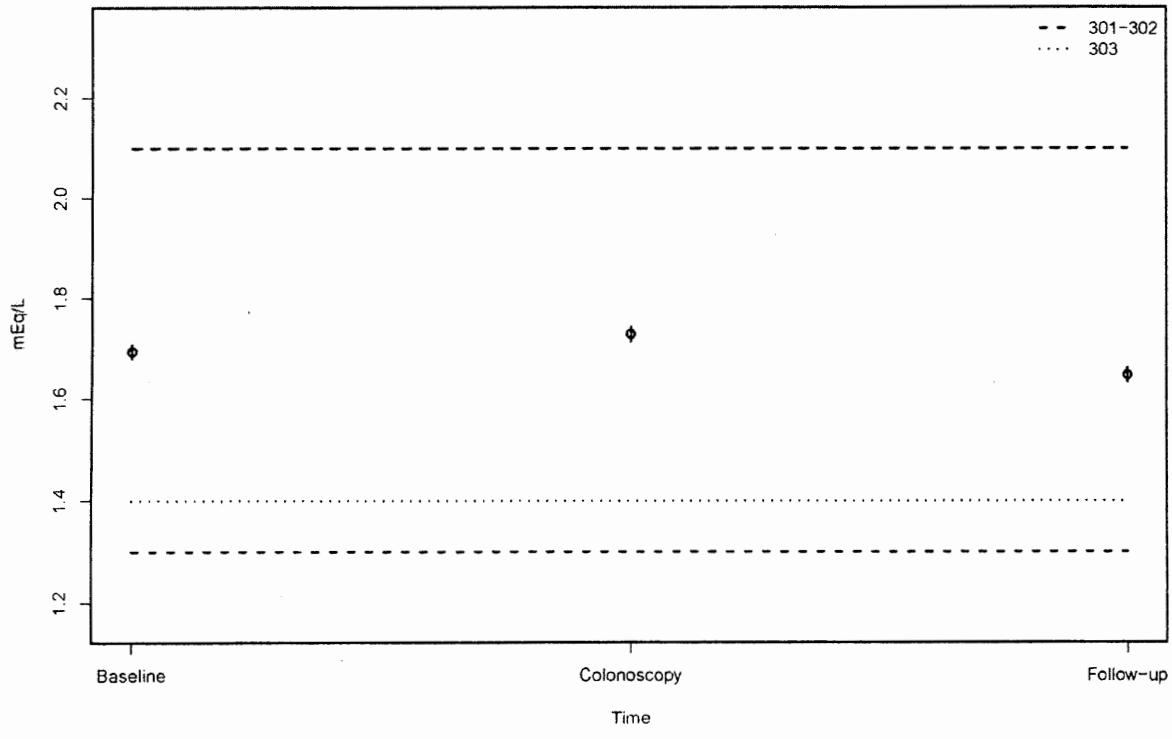
Calcium:



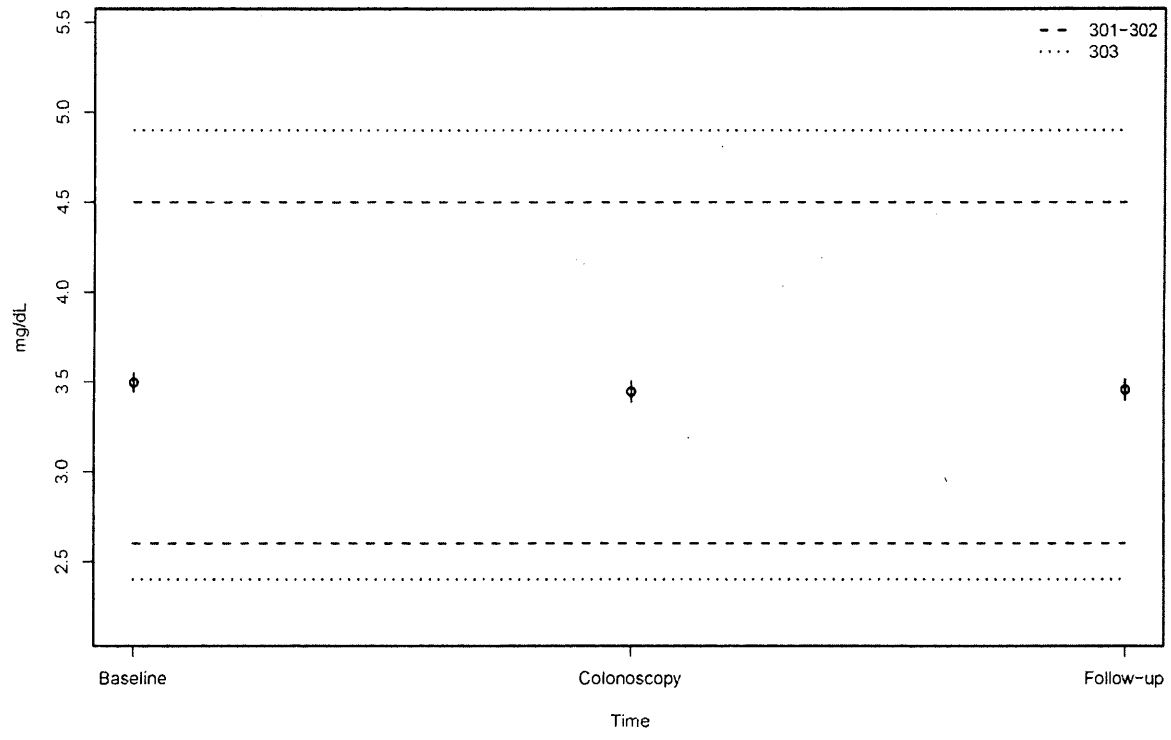
Chloride:



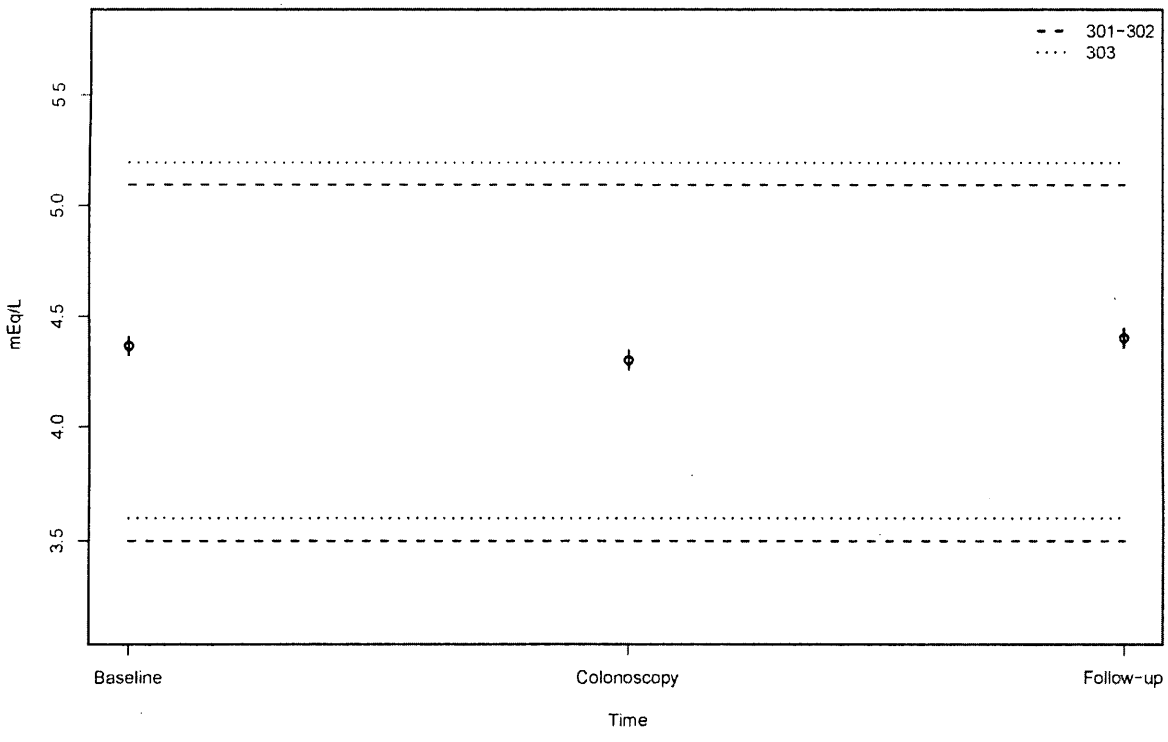
Magnesium:



Phosphate:



Potassium:



61. For BLI800-202, Dr. Heitjan conducted the same analysis as for the BLI800-301, 302, and 303. The 202 study involved multiple blood draws after each administration of SUPREP, and Dr. Heitjan used all time points, as well as the last baseline time point. The confidence interval in the 202 study was somewhat larger than those in the 301, 302, and 303 studies because of the smaller sample size. However, the means in the 202 changed very little between the different time points for each electrolyte, and did not approach the outer limits of the normal range. Tr. 83:13-87:10 (Heitjan Direct); PTX483 (Heitjan SUPREP Analysis) at 1-7; PDX11-44 through 11-50 (Heitjan Slides).

62. The results of Dr. Heitjan's means analysis show that SUPREP did not produce any clinically significant electrolyte shifts in the patient population under the Federal Circuit's claim constructions. Tr. 73:20-74:1; 75:15-20; 76:9-14; 77:8-10; 78:11-17; 79:7-11; 80:15-20; 82:2-9, 85:13-17; 87:2-10 (Heitjan Direct); Tr. 187:25-189:23 (Peura Direct); PTX483 (Heitjan SUPREP Analysis); PDX11-15 through 11-50 (Heitjan Slides).

63. During the original trial, the deletion of phosphate from the colonoscopy preparation was an important safety factor in developing the invention while maintaining efficiency. Dr. Heitjan showed those results.

64. The mean phosphate data for Visicol shows Visicol's profound effect on mean phosphate levels, which moved outside the normal range after administration of the drug. PTX1 ('149 Patent) at 2:40-47; PTX431 (Visicol PDR Entry); PDX11-51 (Heitjan Slides); Tr. 90:17-93:1, 94:15-16 (Heitjan Direct), 191:2-22 (Peura Direct).

65. Dr. Heitjan graphed mean phosphate levels for Phospho-soda based on data from DiPalma 1996 (PTX393). The data shows that Phospho-soda had a profound effect on the mean levels of phosphate, leading to movement of the mean outside the normal range. PDX11-52

(Heitjan Slides); Tr. 93:5-94:14 (Heitjan Direct).

66. The mean phosphate data for Visicol and Phospho-soda show that these products produced clinically significant electrolyte shifts in the patient population – the kinds of clinically significant electrolyte shifts in the patient population that the inventors of the '149 patent sought to avoid with their invention. PTX431 (Visicol PDR Entry); PDX11-51, 11-52 (Heitjan Slides); Tr. 91:24-92:9; 94:9-14 (Heitjan Direct); 191:2-22 (Peura Direct), 568:25-569:15 (Peura Rebuttal Direct); PTX001 ('149 patent) at 2:40-47.

67. A comparison of the mean data from DiPalma 1996[1] and from BLI800-202 shows that Phospho-soda had a profound effect on serum phosphate, while SUPREP had a negligible effect, if any. While the mean moved far outside the range after Phospho-soda administration, it remained within the normal range after SUPREP administration. This comparison makes clear that SUPREP does not cause clinically significant electrolyte shifts in the patient population. PDX11-53 (Heitjan Slides); Tr. 94:17-95:11 (Heitjan Direct); 191:2-22 (Peura Direct).

CONCLUSIONS OF LAW

Infringement

68. Novel's proposed product is identical or "equivalent" to Braintree's SUPREP except for the flavoring. PFOF ¶¶41-42; ECF No. 261 (SJ Op.) at 6. Thus, assuming SUPREP meets the limitations of claims 15 and 18, then Novel's proposed copy infringes those claims. ECF No. 261 (SJ Op.) at 9-10. Utilizing Heitjan's analysis, SUPREP meets each and every limitation of claims 15 and 18. PFOF ¶¶59-171. As a result, Novel's "equivalent" of SUPREP will, if marketed and sold, infringe claims 15 and 18.

[1] The results of the BLI800-303 study were described in a 2010 article by Douglas K. Rex, et al. PTX394 ("Rex 2010"); Tr. 60:20-22 (Heitjan Direct).

69. Finally, Novel will induce infringement of claims 19, 20, and 23, which claim methods for using the compositions of claims 15 and 18. Novel's proposed copy of SUPREP meets each and every limitation of claims 15 and 18. See PFOF ¶¶59-171. Since Novel did not appeal this Court's finding relevant to inducement, there is no reason to change that ruling now. Fed. Cir. Appeal, ECF Nos. 16, 33.

70. Novel's post-trial brief (ECF No. 452) focuses on Braintree's failure to show infringement because of a laundry list of items. From the Court's view, Braintree must prove infringement by a preponderance of the evidence. The Federal Circuit limited the inquiry to whether any clinically significant electrolyte shifts occurred. Here, through the testimony of Dr. Peura and Dr. Heitjan, Braintree has met the burden of proof.

Miscellaneous

71. Novel seeks to sanction Braintree for failure to provide adverse event reports concerning SUPREP administration. Fed. R. Civ. P. 37. Novel argues that "the appropriate sanction for Braintree's failure to produce those documents should be an adverse inference that untoward effects are present in patients to SUPREP has been administered." (Novel Br. (ECF No. 453) at 29.)

72. The Court finds the failure to provide the adverse event reports to be a minor issue that does not require the imposition of an adverse inference. Novel has not shown any prejudice, surprise, or bad faith on the part of Braintree. *See In Re Mercedes*, 225 F.R.D. 498, 506 (D.N.J. 2005). Moreover, such a sanction at this time after a trial and a factual hearing having been completed would constitute a significant but unwarranted disruption to the trial findings. Novel's motion to impose sanctions is denied. The attorneys for the parties conducted themselves professionally and cooperatively during the litigation, and both should be commended for same.

CONCLUSION

The Court finds that Braintree has proved infringement by the preponderance of the evidence. Novel's proposed copy of SUPREP meets each and every limitation of claims 15 and 18, and will therefore infringe upon these claims if marketed and sold. Novel's proposed copy of SUPREP will also induce infringement of claims 19, 20, and 23, which claim methods for using the compositions of claims 15 and 18. Novel's request for an adverse inference is denied. An order will follow.

Dated: June 1, 2015

PETER G. SHERIDAN, U.S.D.J.